

Remarks

Claims 1-47 and 80-83 are pending in the present application. Claims 48-79 were withdrawn by the Examiner from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a non-elected invention. Claims 10, 18, and 31-34 were rejected under 35 USC § 112. Claims 1-7, 9, 12-15, 17, 19-22, 24-28, 30, 32, 35, 36, 39-44, 46, 47, 80, and 83 were rejected under 35 USC § 102(b), and Claims 8, 10, 11, 16, 17, 23, 29, 31, 33, 37, 38, 45, 81, and 82 were rejected under 35 USC § 103(a). Applicants respectfully request reconsideration of the application, withdrawal of all rejections, and allowance of the application in view of the amendments and remarks below.

The Invention

The present invention provides novel methods and devices for generating small particle size, high purity condensation aerosols for delivery of physiologically active compounds. These methods and devices involve heating the physiologically active compound to form a vapor that subsequently cools and condenses into aerosol particles. Among other novel features, the present invention enables precise control of condensation aerosol particle size by controlling the mixing of the vapor with gas. In addition, the present invention teaches the use of gas flow over the vaporizing compound to decrease decomposition of the physiologically active compound during heating. The aerosols produced by this approach advantageously have a lower fraction of decomposition than aerosols produced when the compound is vaporized in the absence of gas flow. These aerosols are especially useful for inhalation therapy, and are capable of delivering pure drug to the lung without simultaneous delivery of unwanted formulation ingredients.

The Amendments to the Claims

Without prejudice to the Applicants' rights to present claims of equal scope in a timely filed continuing application, to expedite prosecution and issuance of the application the Applicants have amended Claims 1, 4 – 12, 16 – 19, 22, 29 – 31, 39, 43, 45, and 81 – 83 to focus the amended claims on methods in which gas flow over a vaporizing compound is utilized to decrease decomposition of the compound. These amendments address the Examiner's concerns as expressed in the Office Action. Applicant also has cancelled Claims 14, 15, 23 – 28, 32, 33, 35 – 42, 44, and 46 – 80. The amended claims are supported by the specification (see below for examples of such support). (The paragraph numbers refer to those in the published application.)

| Claim | Some Examples of Support for the Amended Claims in the Specification |
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| Claim 1 | Paragraphs 0055, 0058, 0059, 0060, 0061, 0112, 0120, 0123 – 0134, Example 1 (note paragraphs 0141, 0142, 0145, 0149, 0159, 0161, 0162, 0163), Example 2, Example 3, Example 4, Example 9 |
| Claim 4 | Paragraph 0145, Example 9 |
| Claim 5 | Paragraphs 0017, 0062, 0106, 0110, 0119, Example 2, Example 9 |
| Claim 6 | Paragraphs 0058, 0059, 0060, 0123 |
| Claim 7 | Paragraphs 0058, 0123, 0125 |
| Claim 8 | Paragraphs 0021, 0106, 0115, 0116 |
| Claim 9 | Paragraph 0121, 0122, 0164 |
| Claim 10 | Example 1 (note paragraphs 0167, 0172, 0174) |
| Claim 11 | Paragraph 0159 |
| Claim 12 | Paragraph 0136 |
| Claim 16 | Paragraph 0228 |
| Claim 17 | Paragraph 0213, Example 3, Example 9 |
| Claim 18 | Paragraphs 0133, 0211, Example 1 (note paragraphs 0141, 0148, 0149, 0150, 0165) |
| Claim 19 | Paragraphs 0055, 0058, 0059, 0060, 0061, 0112, 0120, 0123 – 0132, Example 1 (note paragraphs 0141, 0142, 0143, 0159, 0161, 0162, 0163), Example 2, Example 3, Example 4, Example 9 |
| Claim 22 | Paragraph 0121, 0122, 0164 |
| Claim 29 | Paragraph 0228 |
| Claim 30 | Paragraph 0213, Example 3, Example 9 |
| Claim 31 | Paragraphs 0133, 0211, Example 1 (note paragraphs 0141, 0148, 0149, 0150, 0165) |
| Claim 32 | Paragraphs 0059, 0133, 0134, 0141, 0145, Example 3, Example 4, Example 9 |
| Claim 43 | Example 3, Example 9 |
| Claim 45 | Paragraphs 0133, 0211, Example 1 (note paragraphs 0141, 0148, 0149, 0150, 0165) |
| Claim 81 | Paragraph 0137 |
| Claim 82 | Paragraph 0137 |

The amendments to the claims do not introduce new matter. Applicants respectfully submit that the amendments to the claims put the application in condition for allowance. The Examiner is respectfully requested to enter the amendments to the claims and allow all amended claims.

Claim Objections

The Examiner objected to Claim 71 because of the following informalities: “the preamble of claim 71 is to an apparatus/device, however the body of the claim includes method steps.” Office Action at 2.

Applicants appreciate the Examiner’s careful review of the claim. However, as the Examiner has withdrawn Claim 71, and Claims 72-79 which depend from Claim 71 from further consideration (*Id.*); Applicants note the Examiner’s objection and reserve the right to present amended claims with regard to the objection in a timely filed continuing application.

The Rejection under 35 U.S.C. §112

The Examiner rejected Claims 10, 18, and 31-34 as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In particular, the Office Action stated that “since no function is specified by the word(s) preceding ‘means,’ it is impossible to determine the equivalents of the element...” *Id.* at 3. While the Applicants maintain that the specification contains sufficient description to interpret the claims as originally written, to expedite prosecution Claims 10, 18, and 31 have been rewritten to remove the “means” language. Specifically, Claim 10 has been amended to state that “the establishing a gas flow through the airway is caused by differences in pressure.” Claims 18 and 31 have been amended to state that the “substrate is inductively heated with electrical energy.” Claims 32-34 are amended by the changes to Claim 31, as they depend from Claim 31. Accordingly, the Applicants respectfully request that the Examiner reconsider and withdraw the rejection of these claims under 35 U.S.C. §112.

The Rejection under 35 U.S.C. §102

The Examiner rejected Claims 1-7, 12-15, 17, 19-22, 24 -28, 30, 32, 35, 36, 39-44, 46, 47, 80 and 83 under 35 U.S.C. §102(b) as being anticipated by Gerth et al. 4,735,217. *Id.* at 3. In support of this rejection, the Office Action stated that “Gerth teaches a method for delivering a

physiologically active compound to a patient comprising the steps of: heating the physiologically active compound to a temperature and for a duration that results in an acceptably low level of decomposition; simultaneously passing a gas across the surface of the compound to achieve a desired rate of vaporization; and administering the resulting aerosol to a patient; . . . ” Office action page 3.

The Applicants respectfully disagree with the Examiner’s inferences about Gerth’s teachings. Gerth does not mention “decomposition” nor “an acceptably low level of decomposition.” Note that while Gerth mentions avoiding tars and carbon monoxide which are produced from burning of the non-physiologically active plant constituents of tobacco, Gerth does not address the potential for decomposition upon heating of the physiologically active compound being delivered. In contrast, Applicants’ invention is directed to avoiding thermal decomposition of the physiologically active compound itself, i.e., the Applicants teach methods by which compounds, including “degradable compounds” (US 2003/0051728 A1, paragraph [0011]), with “physiological activity can be volatilized without medicinally significant degradation” (*Id.*, paragraph [0054]). In contrast, Gerth addresses only “combustion free” (Gerth et al. Col. 3, line 38-42) methods of heating the medicament, not methods of preventing decomposition of the medicament itself. Thus, while Gerth does disclose methods of generating heat without producing unwanted byproducts of combustion, only the instant Invention teaches methods for applying heat to a degradable, physiologically active compound without excessively decomposing the physiologically active compound.

Additionally, in the Gerth’s disclosure, the air flow is used to generate an aerosol to reach the lung [“while in the relatively cooler air stream, the vaporized medicament condenses to form tiny aerosol particles that are small enough to enter the user’s lungs . . . Without the moving airstream, the vaporized medicament will merely condense inside the device and will never reach the user’s lungs” (4,735,217 Col. 6, lines 42-50)], and to activate or deactivate the device [“when the air ceases to flow. . . thereby breaking or “opening” the electrical circuit includes resistance heating element 72.” (*Id.* Col. 6, lines 51-65)]. Nowhere does Gerth suggest or disclose “passing a gas across the surface of said compound to achieve a desired rate of vaporization” as is claimed by Applicants in the instant application.

While the Applicants maintain that the claims as originally filed were, for at least the above reasons, not anticipated by Gerth, to expedite prosecution and without prejudice to Applicants’ rights to present claims of equal scope in a timely filed continuing application, Applicants have amended Claims 1 and 19 and cancelled Claims 24, 35, and 80. The amended Claims 1 and 19 are directed to decreasing decomposition of a degradable compound upon heating by use of gas flow over the vaporizing compound. As amended, Claim 1 claims a method for delivering a physiologically active

compound to a patient comprising the following steps: coating onto a substrate a physiologically active compound that when heated in the absence of gas flow detectably decomposes; placing the substrate in an airway, wherein the airway has a cross sectional area such that gas speed over the compound is sufficient to decrease the decomposition of the compound upon heating; establishing a gas flow through the airway; heating the substrate, thereby heating the compound to form a vapor; allowing the vapor to mix into the gas flow, thereby cooling the vapor; allowing the cooled vapor to condense to form an aerosol; and administering the aerosol to a patient. In accordance with the invention, the gas flow over the vaporizing compound results in the aerosol administered to the patient having a lower fraction of decomposition than when the compound is vaporized in the absence of gas flow. Support for this amendment is found throughout the specification and identified above.

As amended, Claim 19 is directed to a method for delivering a physiologically active compound to a patient comprising the steps of heating the physiologically active compound to a temperature that results in substantial vaporization of the compound; simultaneously passing a gas across the surface of the compound; rapidly mixing the vaporized compound into the gas to cool said compound; and administering the resulting aerosol to a patient. In accordance with the invention, the method of Claim 19 contains the claim element that the compound be “contained in a heating-vaporization-mixing zone having a sufficiently restricted cross-sectional area to increase the rate of gas passing across the compound and to achieve a lower level of decomposition than occurs upon vaporization of a similar quantity of the compound at a similar temperature in the absence of gas passing across the compound.”

Gerth fails to teach or disclose a method for delivering a compound that tends to decompose upon heating, or for lowering the level of decomposition that occurs upon vaporization of a compound. Rather Gerth is directed to a device for administering a vaporized medicament at a substantially constant concentration level for any given air flow rate through the device regardless of the time interval which passes between successive inhalations, with a focus on menthol and a speculation on applicability to nicotine. While Gerth mentions avoiding “the tars and carbon monoxide of cigarette smoke” (Gerth et al., Abstract), nowhere does Gerth disclose or suggest concerns about decomposition of the physiologically active compound. Thus, Gerth does not consider the potential for the physiologically active compound to decompose or degrade upon heating, nor does Gerth teach methods of preventing decomposition of compounds that have a propensity to decompose upon heating. In contrast, the instant claims recite the use of airflow to decrease decomposition of compound during vaporization, including use of an airway cross sectional area that serves to decrease such decomposition. The present invention teaches “the use of a reduced

airway cross section increases the speed of the air across the compound's surface" (US 2003/0051728 A1 [0112]) and that because of resulting rapid mixing of the vaporized compound into air, "the vaporized compound was rapidly cooled by exchange of its kinetic energy with kinetic energy of the cooler air; which reduced decomposition" (paragraph [0142]). While Gerth discloses a device having an airway, Gerth does not describe the cross sectional area of the airway, nor its effect on gas speed, nor the importance of gas speed for lowering the fraction of decomposition in the resulting aerosol.

Anticipation requires that "a reference must disclose every element of the challenged claim and enable one skilled in the art to make the anticipating subject matter." PPG Industries, Inc. v. Guardian Industries Corp., 75 F.3d 1558, 1566, 37 USPQ2d 1618, 1642 (Fed. Cir. 1996), see also MPEP §2131 citing Verdegaal Bros. v. Union Oil Co. of California, 2 USPQ2d 1051 (Fed. Cir. 1987). Focusing on amended Claim 1, as Gerth fails to disclose "a physiologically active compound that when heated in the absence of gas flow detectably decomposes;" use of "an airway, wherein the airway has a cross sectional area such that for volumetric gas flows through the airway of 10 – 120 liter per minute, gas speed over the compound is sufficient to decrease the decomposition of the compound upon heating;" and production of "an aerosol, wherein the aerosol has a lower fraction of decomposition than when the compound is vaporized in the absence of gas flow," Gerth cannot be said to anticipate the method of Claim 1. As rejected Claims 2-6, 12-15, 17, 43, and 83 depend or have been amended to depend from Claim 1, these claims are not anticipated for the same reasons. Accordingly, the Applicants respectfully request that the Examiner reconsider and withdraw the rejection of these claims under 35 U.S.C §102(b).

Focusing on amended Claim 19, as Gerth fails to disclose "a heating-vaporization-mixing zone having a sufficiently restricted cross-sectional area to increase the rate of gas passing across said compound and to achieve lower level of decomposition than occurs upon vaporization of a similar quantity of the compound at a similar temperature in the absence of gas passing across the compound," Gerth cannot be said to anticipate the method of Claim 19. As rejected Claims 20-22, 30, and 32 depend from or have been amended to depend from Claim 19, these claims are not anticipated for the same reasons that Claim 19 is not anticipated. Accordingly, the Applicants respectfully request that the Examiner reconsider and withdraw the rejection of these claims under 35 U.S.C §102(b).

In addition to Claims 24, 35, and 80, as noted above, Applicants have canceled Claims 14, 15, 23-28, and 35, 36, 39-42, 44, 46, and 47 to focus prosecution on Claims 1 and 19 and the Claims that depend from them.

The Rejection under 35 U.S.C. §103

The Examiner rejected Claims 16, 17, 29, 31, 37, 38, and 45 under 35 U.S.C. §103 as being unpatentable over Gerth et al. Office Action at page 5. Applicants respectfully disagree in view of the amended claims. Claims 16, 17, and 45 have been modified to depend from amended Claim 1, and Claims 29 and 31 have been modified to depend from amended Claim 19. As amended Claims 1 and 19 each contain claim elements relating to gas flow through an airway with a cross-sectional area that results in gas speed through the airway that decreases decomposition of the compound upon heating. Gerth does not discuss airway cross-sectional area, gas speed, nor compound decomposition, nor the relationship between these parameters, nor the goal of avoiding compound decomposition upon heating. Accordingly Claims 1 and 19 and the claims depending therefrom are not prima facie obvious, as all the claim limitations in these claims are not taught or suggested by Gerth. Claims 37 and 38 have been canceled.

The Examiner rejected Claims 8 and 10 under 35 U.S.C. §103 as being unpatentable over Gerth et al. in view of von Sarela 5,605,146. Office Action at 6. Claims 8 and 10 depend from amended Claim 1. Amended Claim 1 recites a method for delivering a physiologically active compound involving establishing a gas flow through an airway and heating a compound (located within the airway) to form a vapor that condenses to form an **aerosol** that is administered to a patient. (emphasis added). Amended Claim 1 contains the claim element that “gas speed over the compound is sufficient to decrease the decomposition of the compound upon heating.” Modified dependent Claim 8 refers to a mixture of **aerosol** with an additional air stream, and modified dependent Claim 10 refers to a specific method for establishing a gas flow for use in the method of Claim 1. According to the Office Action Sarela teaches “a method of inhalation that uses a common mechanical means” and thus it would be obvious to one of skill in the art “to include the method of using a mechanical means to aid or force circulation of air for breathing/moving vapor.” Office Action page 6. Additionally, the Office Action states that “Gerth/Sarela teaches the method 7 wherein the resulting mixture of the vaporized compound and air is further mixed into an additional air stream to further cool and preclude additional decomposition of the compound.

Applicants respectfully disagree. Sarela is directed to a vaporizer for delivering gaseous anesthetics and not aerosols. Sarela, in describing his methods, states explicitly “and the generation of a gaseous anaesthetic from the liquid anaesthetic, . . . forcing the passage of 0.5-5m³/min. of ambient air along the wall of the chamber to transfer, from the air to the liquid anaesthetic, a quantity of heat that stabilizes the generation of gaseous anaesthetic from the liquid anaesthetic by vaporization of the latter...” U.S. Patent No. 5,605,146, Col. 5-6, lines 56-3. Thus, there would be no motivation to combine Sarela

with Gerth. Additionally, Applicants are confused with the purported disclosure in the Office Action that Gerth/Sarela teach “the resulting mixture of the vaporized compound and air is further mixed into an additional air stream to further cool and preclude additional decomposition of the compound. as set forth in the Office Action. Neither Sarela nor Gerth disclose or address the problem of decomposition of a compound upon heating, nor do these references provide a method to decrease such decomposition.

According to the MPEP § 2143, “to establish a prima facie case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Third, the prior art references (or references when combined) must teach or suggest all the claim limitations.” As Sarela does not teach any form of aerosol delivery, there is no motivation to combine Sarela with Gerth. In addition, as neither Sarela nor Gerth consider the issue of decomposition of a compound upon heating, nor teach methods for decreasing such decomposition, all of the elements of amended Claim 1 are not taught or suggested by these references. Thus, there is no a prima facie case of obviousness.

The Examiner rejected Claim 11 under 35 U.S.C. §103 as being unpatentable over Gerth et al. in view of Howell et al. 5,743,251. Office Action at 6. Claim 11 depends from amended Claim 1, which, as mentioned above, recites a method for delivering a physiologically active compound involving establishing a gas flow through an airway and heating a compound (located within the airway) to form a vapor that condenses to form an aerosol that is administered to a patient. Amended Claim 1 contains the claim element that “the airway has a cross-sectional area such that for volumetric gas flows through the airway of 10 – 120 liter per minute, gas speed over the compound is sufficient to decrease the decomposition of the compound upon heating.” According to the Office Action, “Gerth et al, fails to teach specifically wherein the compound is heated so that the compound vaporizes at the lowest possible temperature;” however, Howell teaches “a method of heating with a common low temperature.” Office Action page 6. Thus, according to the Office Action “it would be obvious to include the method of heating to a low temperature to prevent the compound being heated from becoming unstable.” *Id.*

Applicants respectfully disagree. As stated above, Gerth does not consider the problem of decomposition of a physiologically active compound upon heating the compound to form a vapor, nor does either reference provide methods to decrease such decomposition. Howell does not cure these deficiencies or make obvious in view of Gerth how to accomplish these tasks. Additionally, neither

Gerth nor Howell consider the issue of airway cross-sectional area and its relationship to gas speed over vaporizing compound, nor the implications thereof for compound decomposition. Thus, the Office Action fails to establish even a *prima facie* case of obviousness as each and every element of the invention is not taught or disclosed by these references.

The Examiner rejected Claim 23 under 35 U.S.C. §103 as being unpatentable over Gerth et al. in view of Sprinkel et al. 5,649,554. Office Action at 7. Claim 23 has been cancelled., therefore this rejection is moot. Applicants note, however, that Sprinkel, is deficient in the same manner as discussed above for Gerth and Howell. Therefore, even if Sprinkel were combined with Gerth, there would not be a *prima facie* case of obviousness.

According to the Office Action, Claim 33 was rejected as being unpatentable over Gerth et al. in view of Vinegar et al. 6,632,047. *Id.* The Office Action states that Gerth “fails to teach wherein the foil substrate is stainless steel,” but that Vinegar teaches a common stainless steel substrate for heating and thus it would be obvious to make use of stainless steel because of “its known scientific properties and cost effectiveness.” *Id.*

The Applicants respectfully disagree. Claim 33 depends from amended Claim 19. Claim 19 and certain of its distinguishing features from Gerth are described above. Vinegar is directed to an “in situ thermal desorption soil remediation system.” U.S. Patent No. 6,632,047 B2 (abstract). Vinegar’s invention is not related the field of delivery of physiologically active compounds, nor to the field of aerosol generation, and furthermore provides no teachings related to elements of Claim 19. Thus, there would be no motivation to combine the references to achieve the presently claimed invention, nor is it seen how the combination of the two references would achieve the presently claimed invention.

Furthermore, Applicants’ application teaches that an advantage of stainless steel for use in delivery of a physiologically active compound is that “stainless steel...has a lower thermal conductivity value, without an appreciable increase in thermal mass. Low thermal conductivity is helpful because heat generated by the process needs to remain in the immediate area of interest.” US 2003/0051728 A1 [0135]. The utility of a material with a low thermal conductivity value as applied to generation of aerosol was not taught by Gerth or Vinegar prior to the Applicants’ disclosure. While Vinegar states numerous factors to consider in choosing of metal for heating, in particular “cost, temperature of the soil remediation process, the electrical properties of the metal, the physical properties of the metal, and the chemical resistance properties of the metal” (Vinegar et al., col. 7, lines 15 – 21), Vinegar notably does not teach selecting a metal based on its thermal conductivity properties. Thus, neither the use of stainless steel in a method of delivering a physiologically active compound, nor the rationale for the selection of stainless steel based on its low thermal conductivity,

is taught or suggested by Gerth or Vinegar, and thus there would be no motivation to combine Gerth with Vinegar, nor to select stainless steel out of the wide range of available metals based on the teachings of Gerth or Vinegar.

The Examiner rejected Claims 81 and 82 under 35 U.S.C. §103 as being unpatentable over Gerth et al. in view of Shanbrom et al. 3,949,743. Office Action at 7-8. The Office Action states “Shanbrom teaches a method wherein an aerosol is administered to the eye or the skin for the treatment of disorders, ” thus it would have been obvious “to include the method of administering aerosol to the eye or to the skin for treatment of disorders. Office Action page 8.

Applicants respectfully disagree in light of the amended Claims 81 and 82 and the disclosure in the references. Claims 81 and 82 have been amended to depend from amended Claim 1. Amended Claim 1 recites a method for delivering a physiologically active compound involving establishing a gas flow through an airway and heating a compound (located within the airway) to form a vapor that condenses to form an aerosol that is administered to a patient. Amended Claim 1 contains the claim element that “gas speed over the compound is sufficient to decrease the decomposition of the compound upon heating.” Dependent Claims 81 and 82 refer to administration of the condensation aerosol to the eye and the skin, respectively. Shanbrom does not teach nor suggest the elements of amended Claim 1 which are also absent from Gerth, such as “gas speed” to “decrease decomposition of the compound upon heating.” Rather, Shanbrom is directed to a method of applying a particulate medicament of a type subject to thermal decomposition to an afflicted area involving forming a vapor mist, cooling the vapor mist by directing it through a conduit defining a flow path, and subsequently injecting the medicament in particulate form into the flow path. US Patent No. 3,949,743, col. 7, lines 10-63. In Shanbrom, the medicament subject to thermal decomposition is not heated to form a vapor, but instead is **never exposed to heat** because the vapor into which the **particulate medicament** is injected is first cooled. Thus, Shanbrom conforms to the standard approach within the pharmaceutical industry of **not heating** and therefore **not vaporizing** the medicament subject to thermal decomposition. Thus, Shanbrom teaches away from the present invention in which degradable physiologically active compound **is heated** to form a vapor. As Shanbrom teaches to avoid heating of the medicament, Shanbrom can not be said to teach a method for decreasing the decomposition of the medicament upon heating, such as placing the physiologically active compound coated onto a substrate into an airway, wherein the airway has a cross-sectional area such that gas speed over the compound is sufficient to decrease the decomposition of the compound upon heating, and thus teaches away from the instant invention.

Because Shanbrom teaches away from the present invention, there is no motivation to combine Gerth and Shanbrom. Furthermore, even when combined, neither reference teaches, implies, or in any way suggests the use of "gas speed over the compound...sufficient to decrease the decomposition of the compound upon heating." Thus, while there is no motivation to combine Gerth and Shanbrom, even when combined they fail to teach certain claim elements of Claim 1. Thus, these references fail to render Claim 1 and Claims 81 and 82 which depend from Claim 1 obvious.

Conclusion

The Applicants appreciate the Examiner's careful and thorough review of the application and submit that the Examiner's concerns have been addressed by the amendments and remarks above. The Applicants accordingly request the Examiner to withdraw all rejections and allow the application. In the event the Examiner believes a telephonic discussion would expedite allowance or help to resolve outstanding issues, prosecution of the application, then the Examiner is invited to call the undersigned at (650) 687-3905.

In the unlikely event that the transmittal letter is separated from this document and the Patent Office determines that an extension and/or other relief is required, Applicants petition for any required relief including extensions of time and authorizes the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 502731.**

Respectfully submitted,



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